158

ADDENDUM

ADDICTIVENESS OF NEW SYNTHETIC ANALGESICS

I. Benzimidazole Derivatives:

(a) 1-(Beta-diethylaminoethyl)-2-(benzyl-4-chloro)-5-nitrobenzimidazole (NIH-7586, ARC I-G-1),

(b) 1-(Beta-diethylaminoethyl)-2-(p-ethoxybenzyl)-5-nitrobenzimidazole methane sulfonate (NIH-7607, ARC I-G-2),

II. (-)-3-Hydroxy-N-(3,3-dimethylallyl)-morphinan hydrobromide (NIH-7446), ARC, I-B-19

III. N-(1-Methyl-2-piperidinoethyl)-propionanilide hydrochloride (Phenampromid), and (NIH-7602, ARC I-I-1)
N-[2-([Methyl]-phenethylamino)-propyl]-propionanilide sulfate (Diampromid). (NIH-7603, ARC I-J-1)

By

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B-229

I. Benzimidazole Derivatives

Data on the two benzimidazole derivatives (hereinafter designated NIH-7586 and NIH-7607) is abstracted from a report by Isbell and Fraser (unpublished).[1] Hunger et al.[2] and Gross and Turrian[3] have found that some basically substituted benzimidazole derivatives have analgesic activity. In addicted monkeys, NIH-7586 was twice, and NIH-7607 was 1500 times as potent as morphine in alleviating abstinence.[4] Since these compounds constituted a completely new chemical class of analgesics, NIH-7586 and NIH-7607 were referred to the Addiction Research Center, U. S. Public Health Service Hospital, Lexington, Kentucky, for determination of their addictive potentialities in man.

Methods

Because of reports of respiratory depression after parenteral administration, the oral route was used exclusively. NIH-7586 was given in the form of compressed tablets, each containing 25 mg. NIH-7607 was administered in a solution in distilled water in concentrations of 0.01 and 0.1 mg/ml. Drugs were administered to patients in a fasting state. Identity of the drugs was unknown to the patients but was known to the observers ("single-blind").

Effects of Single Doses of NIH-7586 and NIH-7607.

Observations were made one, two, three, four, six, eight, ten, twelve and fourteen hours after medication and included subjective effects as tabulated from questionnaires, measurements of pupillary diameter and recording of morphine-like behavior.[5] Thirteen subjects received NIH-7586 and 7 subjects received NIH-7607 and the effects observed were compared with those obtained in 14 subjects who received 20 and 30 mg of morphine, 60 and 90 mg of codeine, and a placebo (all orally) in another experiment.

Suppression of abstinence was evaluated in 5 patients who were stabilized on 60 mg of morphine sulfate administered subcutaneously four times daily.[5] NIH-7586 and NIH-7607 were substituted orally for morphine in amounts thought, on the basis of preliminary experiments, to be approximately equivalent to 10 to 40 percent (18 to 72 mg) of the patient's accustomed dose of morphine. In the case of NIH-7586, the dosages selected were 75 and 150 mg divided into three doses during the 24 hours. In the case of NIH-7607, the dosages chosen were 0.15 and 0.3 mg, likewise divided into three doses during the 24 hours. Data were compared with those obtained in another experiment in which 9 patients received 18 mg (10 percent of their accustomed dose), 36 mg (20 percent), and 90 mg (50 percent) of morphine sulfate subcutaneously in similar tests. Regression lines, estimates of potency of NIH-7586 and NIH-7607 given orally as compared with the potency of morphine given subcutaneously, and 95 percent confidence limits were calculated according to the method described by Bliss.[6]

A "short" (18 day), "double-blind," direct addiction test was carried out on NIH-7607, and its addictiveness by the oral route was compared with that of morphine, heroin and a placebo, the latter three medications being administered subcutaneously. The methods employed are described elsewhere by

Fraser, Isbell, Van Horn and Martin.[7] Eight nontolerant former opiate addicts were used, and each was exposed to all drugs. The average initial daily dosage of each drug was as follows: morphine, 30.6; heroin, 13.0; and NIH-7607, 0.383 mg. The dosage of each drug was progressively accelerated and the final average daily dosage attained on the 18th day was as follows: morphine, 207.0; heroin, 86.8; and NIH-7607, 2.95 mg. All drugs were abruptly withdrawn and identically appearing placebos substituted. Observations for intensity of abstinence were made for ten days according to the method of Kolb and Himmelsbach employing a "standard" and a "modified" Himmelsbach scoring procedure.[5] Once daily throughout the experiment, a "Chronic Dosage Attitude" questionnaire for opiates (patients' ratings) and a parallel "Chronic Dosage Attitude" questionnaire for aides (observers' ratings) were completed.[8]

Results

Effects of Single Doses. The results as presented in Tables 1 and 2 are compared with those obtained with 20 and 30 mg of morphine sulfate orally, and with 60 and 90 mg of codeine sulfate orally in another experiment. Both drugs induced typical morphine-like "euphoria" and behavior. NIH-7586 appears to be roughly one-third to one-fifth as potent as morphine, and roughly equivalent to codeine in this respect. NIH-7607 appears to be more than 80 to 120 times as effective as morphine orally as an "euphoriant."

Suppression of Abstinence. Both NIH-7586 and NIH-7607 partially suppressed abstinence from morphine in the doses used. The results shown in Figure 1 indicate that 1 mg of morphine subcutaneously was equivalent to 2.62 (1.00-6.59) mg of NIH-7586 orally, and 1 mg of NIH-7607 orally was equivalent to 59.3 (15.55 to 136.5) mg of morphine subcutaneously. The curves met the standard requirements for significance of slope and parallelism. The figures in parentheses are the 95 percent confidence limits.

"Short," "Double-Blind," Direct Addiction Tests (NIH-7607 Orally; Morphine and Heroin Subcutaneously). In 6 of 8 patients, no difficulty was encountered in progressively accelerating the dosage of drugs. However 2 patients were quite intolerant to all drugs when the dosage was augmented. For example, the maximum daily dosage of heroin attained by the 18th day for one patient was 41.5 mg, and the other 48 mg; whereas 5 other patients reached a dose of 103 mg daily, and one 90 mg daily. The results of tabulating the "Attitude" questionnaires for opiates, employing both patients' and aides' ratings, are shown in Figure 2. Whereas heroin and morphine were consistently identified as "dope," NIH-7607 was frequently not so classified and many of the patients identified it as being "dope" and "goof balls" (barbiturates) concurrently. It is noteworthy however that the

aides considered that the pattern of effects objectively resembled those of an opiate and were not impressed by the "non-opiate" characteristics of NIH-7607. Insofar as "estimate of strength" is concerned, patients considered the effects of NIH-7607 quite weak, since the average score on the weighted scale was only 1.0, whereas morphine and heroin rated about 3.5. In response to the question, "would you like to take the drug daily?" only 16 percent of the responses indicated they would like to take NIH-7607 daily, whereas 32.6 percent indicated they would like to take heroin daily, and 42 percent, morphine daily (It should be pointed out that U.S. addicts prefer to take their drugs by injection, and this may account in part for the subjects' relatively low acceptance rate for NIH-7607, which was administered orally in this study). The low incidence of positive responses following a placebo, in the ratings by both patients and aides, is noteworthy since no attempt was made to eliminate placebo responders in the selection of subjects.[7] When all three drugs were abruptly discontinued and replaced by a placebo, a moderately severe abstinence syndrome ensued during the next ten days and, as shown in Figure 3, the severity of abstinence as judged by the total daily point scores was very similar for morphine, heroin, and NIH-7607. The patients, however, considered that abstinence

from NIH-7607 was somewhat less severe than that which followed withdrawal of subcutaneously administered morphine and heroin; this might be in part due to a more gradual onset of symptoms when drugs given orally are discontinued. These experiments indicate that a very high degree of physical dependence, comparable to that produced by morphine and heroin, develops when NIH-7607 is administered chronically on an abusive schedule.

Summary

1. The addiction liability of orally administered 1-(Beta-diethylaminoethyl)-2-(benzyl-4-chloro)-5-nitrobenzimidazole (NIH-7586) and 1-(Beta-diethylaminoethyl)-2-(p-ethoxybenzyl)-5-nitrobenzimidazole methane sulfonate (NIH-7607) has been investigated in man.

2. In single doses both NIH-7586 and NIH-7607 induced morphine-like subjective effects and behavior in nontolerant former morphine addicts. NIH-7586 is one-fifth to one-third as potent as oral morphine in inducing subjective effects, whereas NIH-7607 is 80 to 120 times as potent as morphine in this respect. Both drugs constrict the pupils.

3. Both NIH-7586 and NIH-7607 suppress symptoms of abstinence from morphine.

B-222

4. When NIH-7607 was given in a direct addiction study the overall pattern observed during chronic administration and following withdrawal resembled that of patients given morphine or heroin. Although identified as an opiate, patients were much impressed by the hypnotic actions of this drug.

It is concluded that NIH-7586 and NIH-7607 have addictive potentials comparable to that of morphine.

II. 1-3-Hydroxy-N-(3,3-dimethylallyl)-morphinan hydrobromide.

This compound, developed by Hoffman-La Roche and hereinafter designated as NIH-7446, is structurally related to levallorphan. Nalorphine, although an effective analgesic, provokes disturbing mental effects which preclude its use as an analgesic. Therefore an effort has been made to find nonaddicting compounds of the nalorphine type with fewer undesirable side effects. One of these, NIH-7446, was referred for study.

Keats found that NIH-7446 was as potent as morphine as an analgesic in relieving postoperative pain, but, when given in equivalent analgesic doses to normal subjects, was only half as potent as morphine in depressing respiration.[9] However in another experiment, in 3 patients, high doses (1 mg/kilo) of NIH-7446 provoked respiratory depression which was equivalent to that induced by morphine and which was dramatically antagonized by nalorphine.[9]

In comparison with nalorphine, the morphine-antagonistic properties of NIH-7446 are not prominent. Thus Keats found that NIH-7446 produced little antagonism in 3 patients who had received morphine (1 mg/kg).[9]

In the following presentation, the addictiveness of NIH-7446 will be evaluated from the viewpoints of (1) the effects of single doses, (2) its antagonistic properties in morphine-dependent subjects, and (3) its ability to suppress symptoms of abstinence in morphine-dependent patients.

Methods

Effects of Single Subcutaneous Doses of NIH-7446 (10 and 15 mg) as Compared with Corresponding Doses of Morphine Sulfate. Effects were evaluated in a "single-blind," cross-over experiment employing 9 nontolerant former opiate addicts, each of whom received in a randomized order at weekly intervals 10 and 15 mg of NIH-7446, and 10 and 15 mg of morphine sulfate. Observations were made 1/2, 1½, 2½, 3½, 5½ and 7½ hours after medication. These included responses to the "Single Dose Attitude" questionnaire (patients' ratings),[8] "Single Dose Attitude" questionnaire (observers' ratings),[8] and measurements of the pupillary diameter made in a room with controlled lighting.[5] In tabulating the data emphasis was placed on the incidence of "opiate" symptoms and the extent to which these former addicts "liked" the medication, as evaluated in a weighted scale.

24-Hour Substitution of NIH-7446 for Morphine, as Compared with Morphine Continued, and with a Placebo. Nine addicted patients, who were stabilized on an average of 240 mg of morphine sulfate daily, received as a substitute an average of 200 mg of NIH-7446 (divided among four equal subcutaneous doses). This was compared with 180 mg of morphine sulfate and a placebo continued in the same patients[5] (Note that only three injections of 60 mg each of morphine sulfate, or a total of 180 mg during the interval of substitution, is equivalent to 240 mg of morphine sulfate daily, since the fourth injection of morphine is due at the end of the 24 hours).

Observations for intensity of abstinence were made from the 14th through the 24th hour of substitution, and the total abstinence scores for eleven hours (TAS-11) were calculated according to the method of Winter and Flataker.[10] The paired t-test, using each individual as his own control, was employed to determine whether there was a significant difference in the TAS-11 scores for NIH-7446, morphine, and placebo.[11]

Antagonistic (Nalorphine) Characteristics were evaluated by administering 2 to 20 mg of NIH-7446 subcutaneously to 5 patients chronically receiving 240 mg of morphine sulfate daily. NIH-7446 was given two to three hours after the last subcutaneous injection of morphine and patients were observed for signs of abstinence from morphine.

Results

Effects of Single, Subcutaneous Doses of NIH-7446 (10 and 15 mg), as Compared with Corresponding Doses of Morphine Sulfate. All 9 patients identified both morphine sulfate and NIH-7446 as being "dope," and, as shown in Figure 4, the incidence of "opiate-like" symptoms and degree of "liking" for both drugs were very similar when the same doses were given (These observations are in accordance with those of Keats in respect to the relative analgesic potency of morphine and NIH-7446).

24-Hour Substitution of NIH-7446 for Morphine, as Compared with Morphine Continued, and with a Placebo. NIH-7446 substituted very satisfactorily for morphine in a relative dosage of 200 mg of NIH-7446 for 180 mg of morphine. However the curve was not as flat as that observed when morphine was continued, and the difference between these curves is significant ($P \leq 0.001$, Figure 5). On the other hand, NIH-7446 suppressed abstinence significantly better than did a placebo ($P < 0.001$, Figure 5). It is concluded that in the dosage employed NIH-7446 effectively, but incompletely, suppressed symptoms of abstinence from morphine.

Antagonistic (Nalorphine) Characteristics. No evidence of any effect was observed when 2 to 10 mg of NIH-7446 was administered to morphine-dependent patients. However, the patients stated that when the dosage was increased to 20 mg there might have been a slight "boost" in opiate-like effects. There was no evidence of precipitation of abstinence by administration of NIH-7446 in any of the tests.

Summary

It is concluded from these studies that the qualitative and quantitative effects of NIH-7446 are very similar to those of morphine, and its addictiveness probably approaches that of morphine.

III. (a) N-(1-Methyl-2-piperidinoethyl)-propioanilide hydrochloride (Phenampromid), and

(b) N-[2-([Methyl]-phenethylamino)-propyl]-propioanilide sulfate (Diampromid).

These drugs (Phenampromid and Diampromid) were developed by Wright, Brabander and Hardy.[12] The analgesic potency of Phenampromid equalled that of codeine in mice, and meperidine in rats. Diampromid approximated the analgesic potency of meperidine in mice, and of morphine in rats.[13] Nalorphine antagonized the analgesic and respiratory depressant actions of both compounds,[13] and both were effective analgesics in preliminary trials in man.[14]

The methods used for evaluating the addictiveness of these compounds in man were similar to those enumerated for NIH-7446, except that when single doses were administered incomplete comparisons were made with morphine administered to the same subjects.

For convenience in presentation, the results obtained with the two drugs will be presented separately.

Results. (a) Phenampromid

Effects of Single, Subcutaneous Doses of Phenampromid. These were evaluated using the "Single Dose Attitude" questionnaire (patients' ratings)[8] in sixteen tests in a dose range of 10 to 200 mg. Observations were carried out 1/2, 1½, 2½, 3½, 5½ and 7½ hours after medication. Definite opiate-like subjective effects were reported with doses of 75 mg. Six patients received 200 mg. In this dosage, one patient liked the drug "slightly," four, "moderately," and one, "an awful lot."

Suppression of Abstinence from Morphine with Phenampromid was evaluated in the same 9 subjects used in the studies on NIH-7446. For comparative purposes, 24-hour substitutions were also carried out with morphine (positive control) and a placebo (negative control) on each subject. The average dosage

administered during the 24 hours was 1135 mg, divided among three approximately equal subcutaneous doses. At the conclusion of the substitution each patient completed the "Chronic Dosage Attitude" questionnaire (patients' ratings).[8] The intensity of abstinence was measured hourly from the 14th through the 24th hour during the interval of substitution, using the "modified" Himmelsbach hourly point score.[5] Although, during the substitution, 4 of the 9 patients identified Phenampromid as being "dope," all emphatically stated they did not like the effects of the medication. They complained that it gave them a "weird feeling" which they had not experienced previously, and compared its effects with those of lysergic acid diethylamide (LSD-25), cocaine, or marihuana.

Abstinence phenomena were partially, but significantly, suppressed by Phenampromid (Figure 5). Because of the disturbing side effects it was not feasible to employ larger doses of Phenampromid in order to evaluate the pharmacological equivalence of morphine and Phenampromid more completely.

Results. (b) Diampromid

Effects of Single Subcutaneous Doses of Diampromid were evaluated in twelve tests in a dose range of 5 to 75 mg, using the "Single Dose Attitude" questionnaire (patients' ratings) and the parallel questionnaire for observers' ratings. With doses of 50 and 75 mg, very typical "subjective" morphine-like effects were reported by the patients and characteristic morphine-like behavior was observed by the aides. A dose of 75 mg was considered to be roughly equivalent to 20 mg of morphine subcutaneously. Although peak effects were similar to those of morphine, all patients complained that the medication had a short duration of action, and this was substantiated by pupillary measurements, which indicated that maximum miosis persisted for only two and one-half to three hours.

Effects of Single Intravenous Doses of Diampromid were evaluated in a pilot study using dosages as follows: 20 mg (1 subject), 25 mg (2 subjects), and 75 mg (1 subject). "Single Dose Attitude" questionnaires were completed by both the subjects and observers, and the pupillary diameter was measured at intervals as described for single subcutaneous doses. In these doses, all subjects consistently identified the medication as "dope" and the extent to which they liked the

medication ranged from "slight" to "a lot." The patient who received 75 mg of Diampromid became pale one minute after the injection and had difficulty walking to the observation room. He sat on a chair and very promptly fell asleep. He was given 10 mg of nalorphine intramuscularly about four minutes after the injection of Diampromid, and recovered rapidly. No further injections of nalorphine were required.

Suppression of Abstinence from Morphine with Diampromid was evaluated in the same 9 subjects employed for Phenampromid, using the same controls and methods of observation. A dose of 750 mg (divided among four equal doses) was substituted for morphine in 8 of these subjects, and in one subject a dose of 625 mg, similarly divided, was used. Diampromid substituted quite adequately for morphine in this dosage, but the chief complaint of the patients was: "it only holds you for about two hours." This observation is confirmed by the intermittent peaking of the abstinence scores, and in each instance abstinence symptoms were promptly relieved by medication (note the arrows in Figure 5). In the case of Diampromid, the total TAS-11 score was significantly greater than that observed when morphine was continued in the same patients, but the ability

of Diampromid to suppress abstinence from morphine was inadequately tested, since medication would need to be given at more frequent intervals.

Summary

Both Phenampromid and Diampromid possess addiction liability. These experiments, however, are insufficient to assess their relative addictiveness as compared to morphine and codeine.

References

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8. Fraser, H. F. and Isbell, H.: Human Pharmacology and Addictiveness of Ethyl 1-(3-Cyano-3,3-phenylpropyl)-4-phenyl-4-piperidine carboxylate hydrochloride (R-1132, Diphenoxylate). Addendum . Min. 21st Meeting Comm. on Drug Addiction and Narcotics. Natl. Res. Council. Washington, D. C. Natl. Acad. Sci. (Jan.) 1960.

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10. Winter, C. A. and Flataker, L.: Studies on Heptazone (6-Morpholino-4,4-Diphenyl-3-Heptanone Hydrochloride) in Comparison with other Analgesic Agents. J. Pharmacol. & Exper. Therap., 98: 305-317 (Mar.) 1950.

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14. Place, V. A.: Personal communication.

Table 1

"Subjective" characterization of NIH-7586 and NIH-7607 as compared with morphine, codeine and a placebo, all administered orally.+

Drug	Dose (mg)	No. of Subjects	Number of Patients Responding: Positive for Opiates	Positive for other Drugs	Questionable	Negative
NIH-7586	100	13	5	1	3	4
NIH-7607	0.25	7	6	1	0	0
Morphine *	20	14	7	1 [1]	3	3
Morphine *	30	14	7	2	3	2
Codeine *	60	14	5	1 [1]	4	4
Codeine *	90	14	6	1	5	2
Placebo *	--	14	1	[1]	1	12

\+ For method of scoring, see Reference No. 5.

[] Figures in brackets represent patients who also reported positively for opiates.

* Data from another experiment.

B-209

Table 2

Pupillary constriction after NIH-7586 and NIH-7607, as compared with morphine, codeine and a placebo, all given orally.

Drug	Dose (mg)	No. of Subjects	Mean Area Under Curve (Mm Hours ± S.E.)
NIH-7586	100	13	8.14 ± 0.81
NIH-7607	0.25	7	10.9 ± 1.35
Morphine *	20	14	11.4 ± 2.5
Morphine *	30	14	17.1 ± 3.2
Codeine *	60	14	9.0 ± 1.7
Codeine *	90	14	14.4 ± 2.4
Placebo	—	14	0.4 ± 1.63

* Data from another experiment.

B-208

Legend for Figure 1.

Figure 1. Dose-effect curves and relative potency for suppression of abstinence from morphine by NIH-7607 and NIH-7586 as compared with graded doses of morphine; 24-hour substitutions in addicted individuals stabilized on 240 mg of morphine per day.

B-206

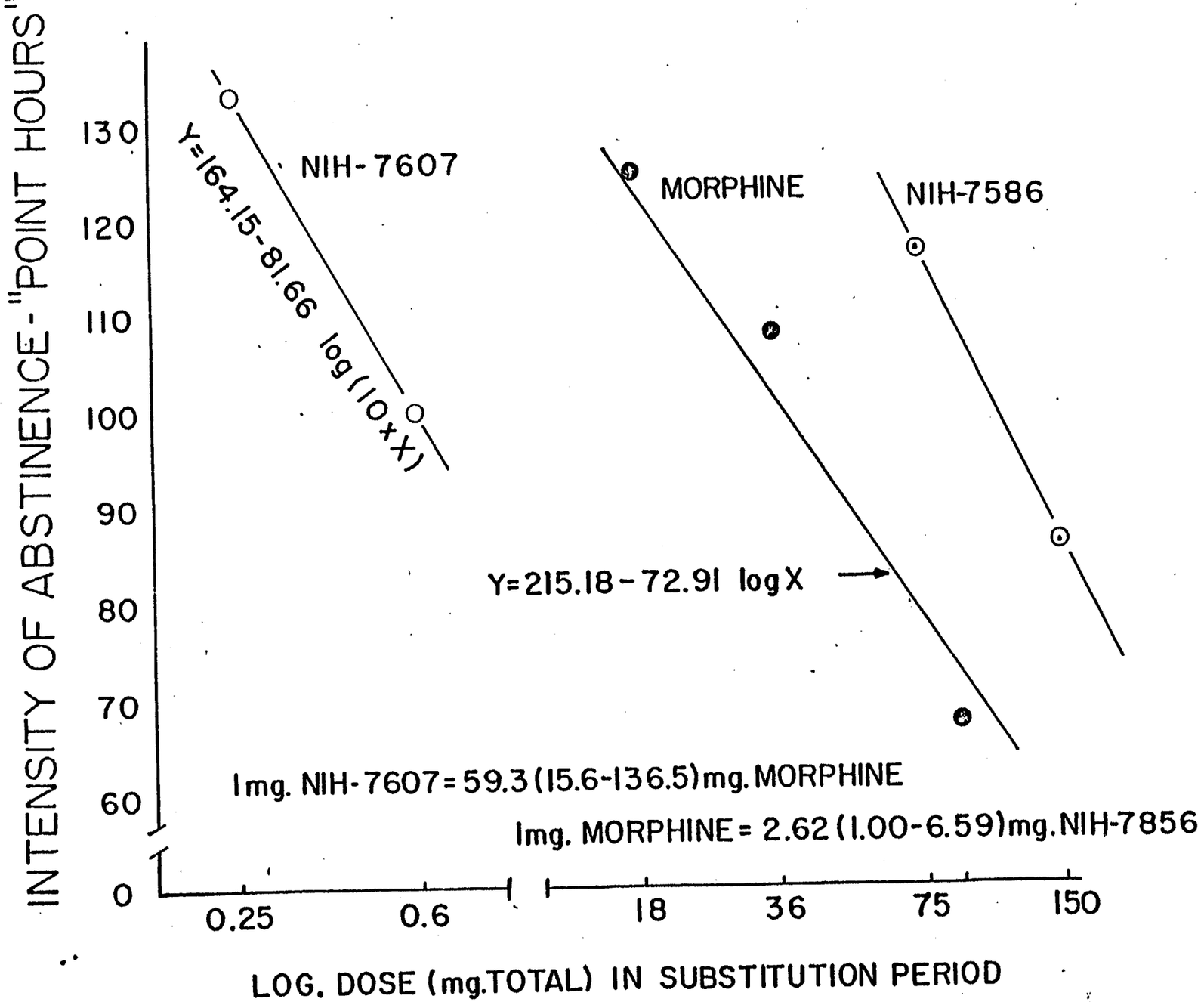
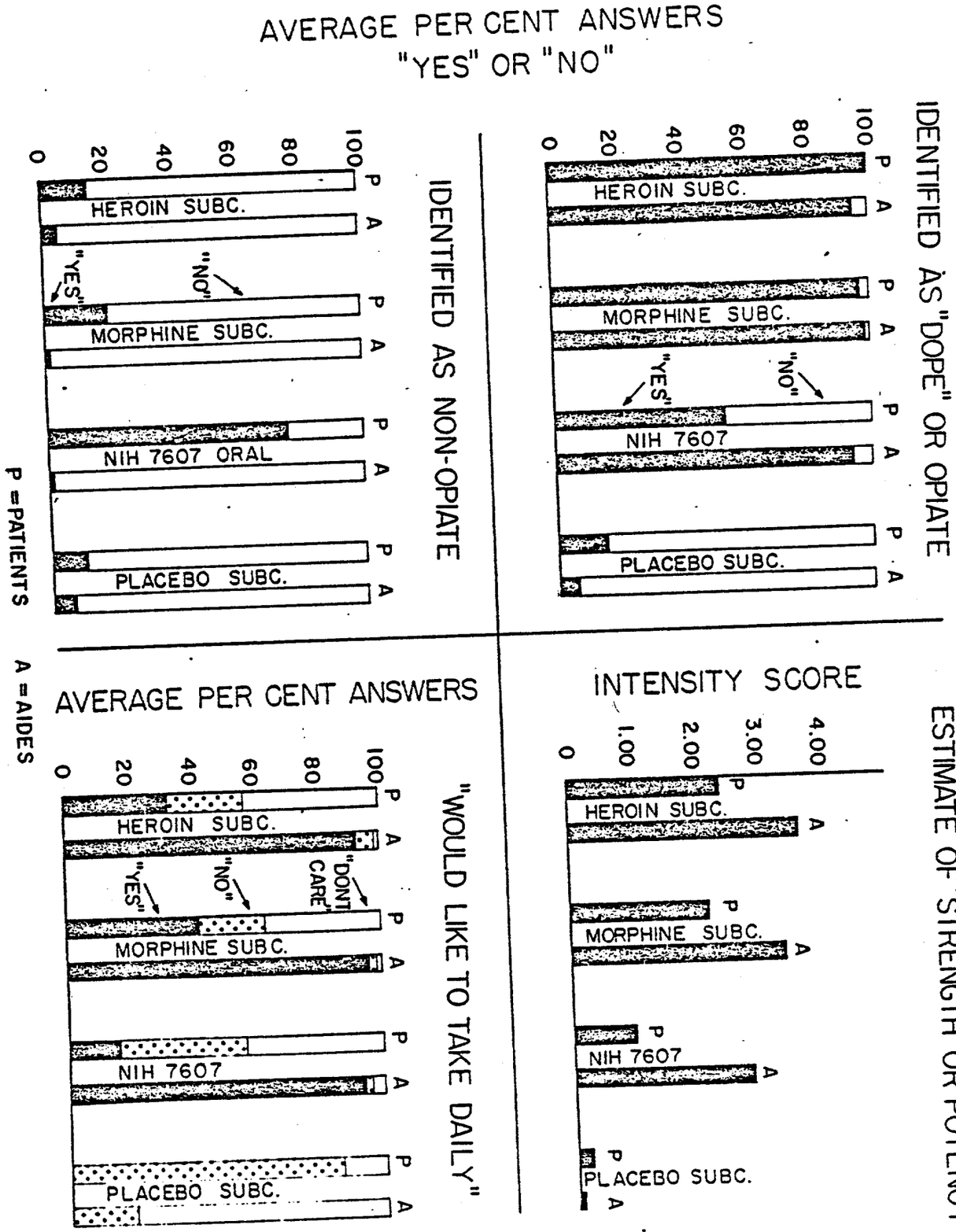

INTENSITY OF ABSTINENCE-"POINT HOURS"
130
120
110
100
90
80
70
60
0
NIH-7607
Y=164.15-81.66 log(10xX)
MORPHINE
NIH-7586
Y=215.18-72.91 log X
1mg. NIH-7607=59.3(15.6-136.5)mg. MORPHINE
1mg. MORPHINE=2.62(1.00-6.59)mg. NIH-7856
0.25
0.6
18
36
75
150
LOG. DOSE (mg.TOTAL) IN SUBSTITUTION PERIOD

Figure 1. Addictiveness of New Synthetic Analgesics.

DAC Report, January 1960.

Legend for Figure 2.

Figure 2. Summary of the results of "Chronic Dosage Attitude" Questionnaires independently completed by patients (patients' ratings) and aides (observers' ratings) when they evaluated the effects of heroin, morphine, NIH-7607, and a placebo during an 18-day, "double-blind," direct addiction study.

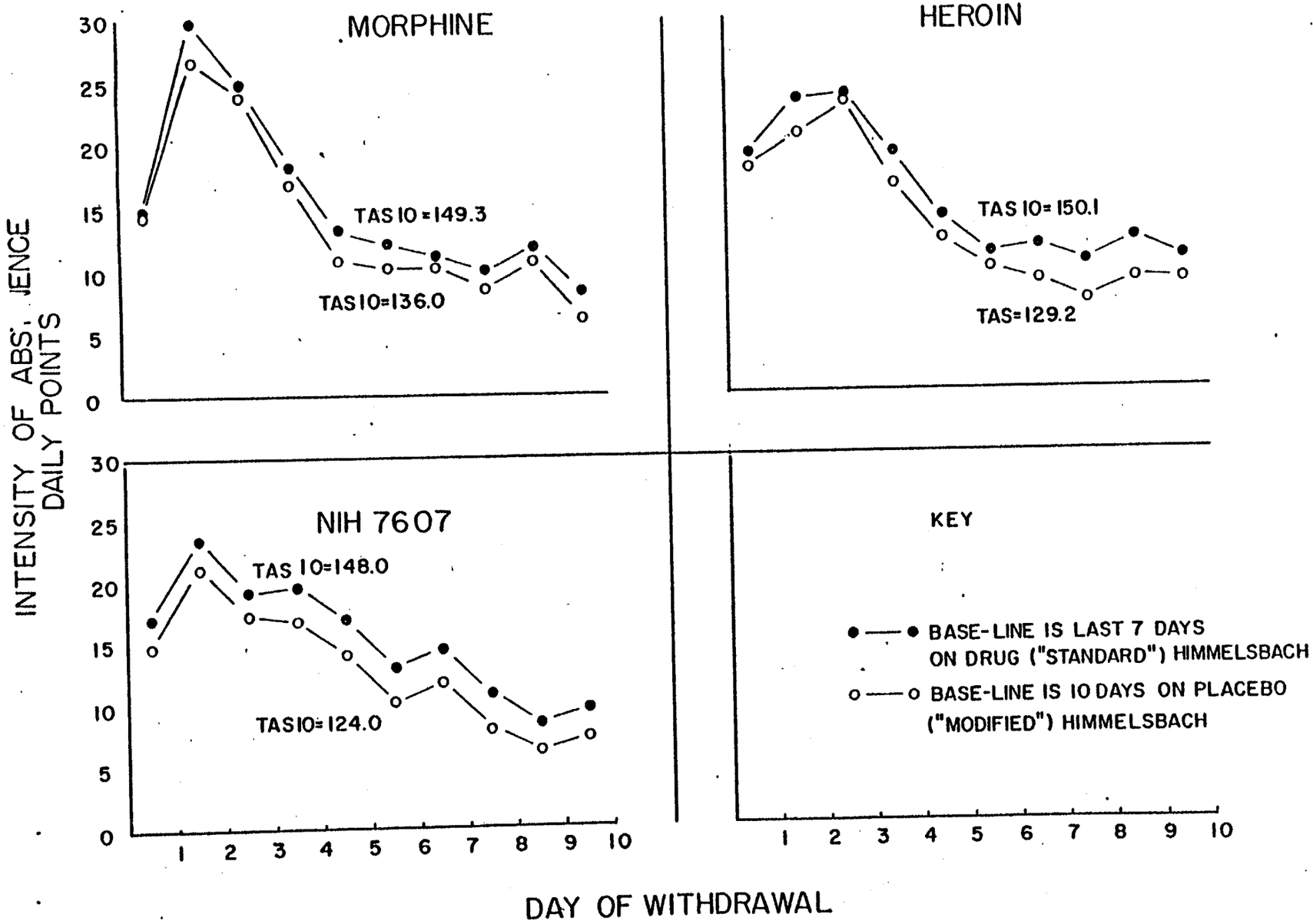

AVERAGE PER CENT ANSWERS
"YES" OR "NO"
IDENTIFIED AS NON-OPIATE
IDENTIFIED AS "DOPE" OR OPIATE
"WOULD LIKE TO TAKE DAILY"
ESTIMATE OF "STRENGTH" OR POTENCY
AVERAGE PER CENT ANSWERS
INTENSITY SCORE
0
20
40
60
80
100
1.00
2.00
3.00
4.00
HEROIN SUBC.
MORPHINE SUBC.
NIH 7607 ORAL
NIH 7607
PLACEBO SUBC.
"YES"
"NO"
"DONT CARE"
P
A
P = PATIENTS
A = AIDES

B-204

Legend for Figure 3.

Figure 3. Comparative intensity of abstinence after abrupt withdrawal of morphine, heroin, and NIH-7607. Daily point scores were computed by using the averages for rectal temperature, respiratory rate, blood pressure and caloric intake observed during 10 days on placebo ("modified" Himmelsbach procedure), and the "standard" Himmelsbach procedure in which the above variables were computed from those observed during the last seven days on drug. The TAS-10 values represent the mean areas (total intensity of abstinence for 10 days).

B-202

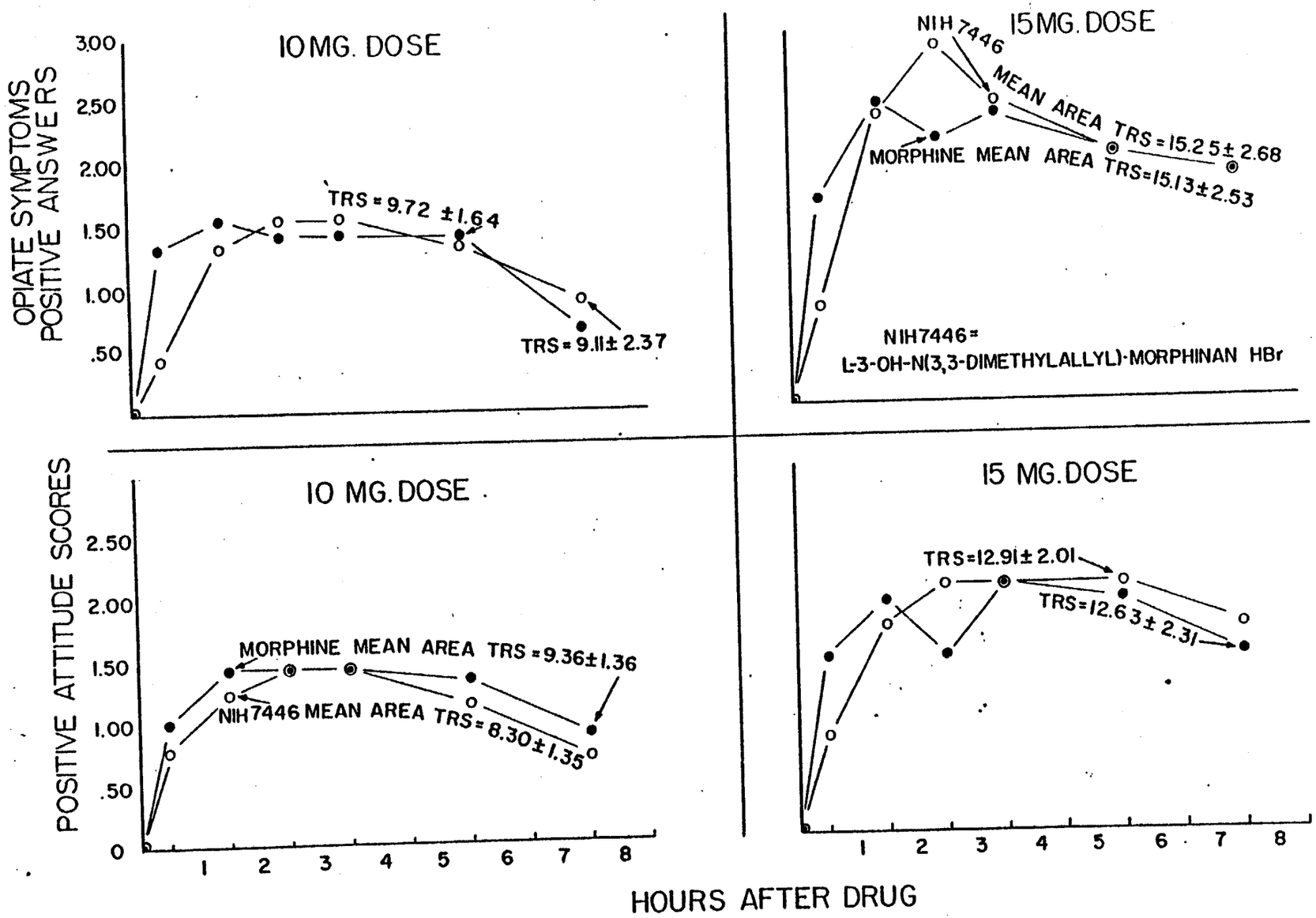

MORPHINE
TAS 10 = 149.3
TAS 10=136.0
HEROIN
TAS 10= 150.1
TAS=129.2
NIH 7607
TAS 10=148.0
TAS10= 124.0
KEY
BASE-LINE IS LAST 7 DAYS ON DRUG ("STANDARD") HIMMELSBACH
BASE-LINE IS 10 DAYS ON PLACEBO ("MODIFIED") HIMMELSBACH
INTENSITY OF ABS. JENCE DAILY POINTS
0
5
10
15
20
25
30
1 2 3 4 5 6 7 8 9 10
DAY OF WITHDRAWAL

Legend for Figure 4.

Figure 4. Comparative effects of 10 and 15 mg of morphine sulfate and 10 and 15 mg of NIH-7446 (patients' ratings) in respect to the incidence of opiate symptoms (maximum possible positive answers hourly = 7.0); and a weighted attitude score (maximum possible hourly score = 4.0). "TRS" values represent the mean areas (total response scores for 7½ hours) ± standard areas of the mean. It should be noted that morphine and NIH-7446 showed very similar effects in respect to these variables. There was a tendency for the effects of morphine to develop more rapidly than did those of NIH-7446.

B-200

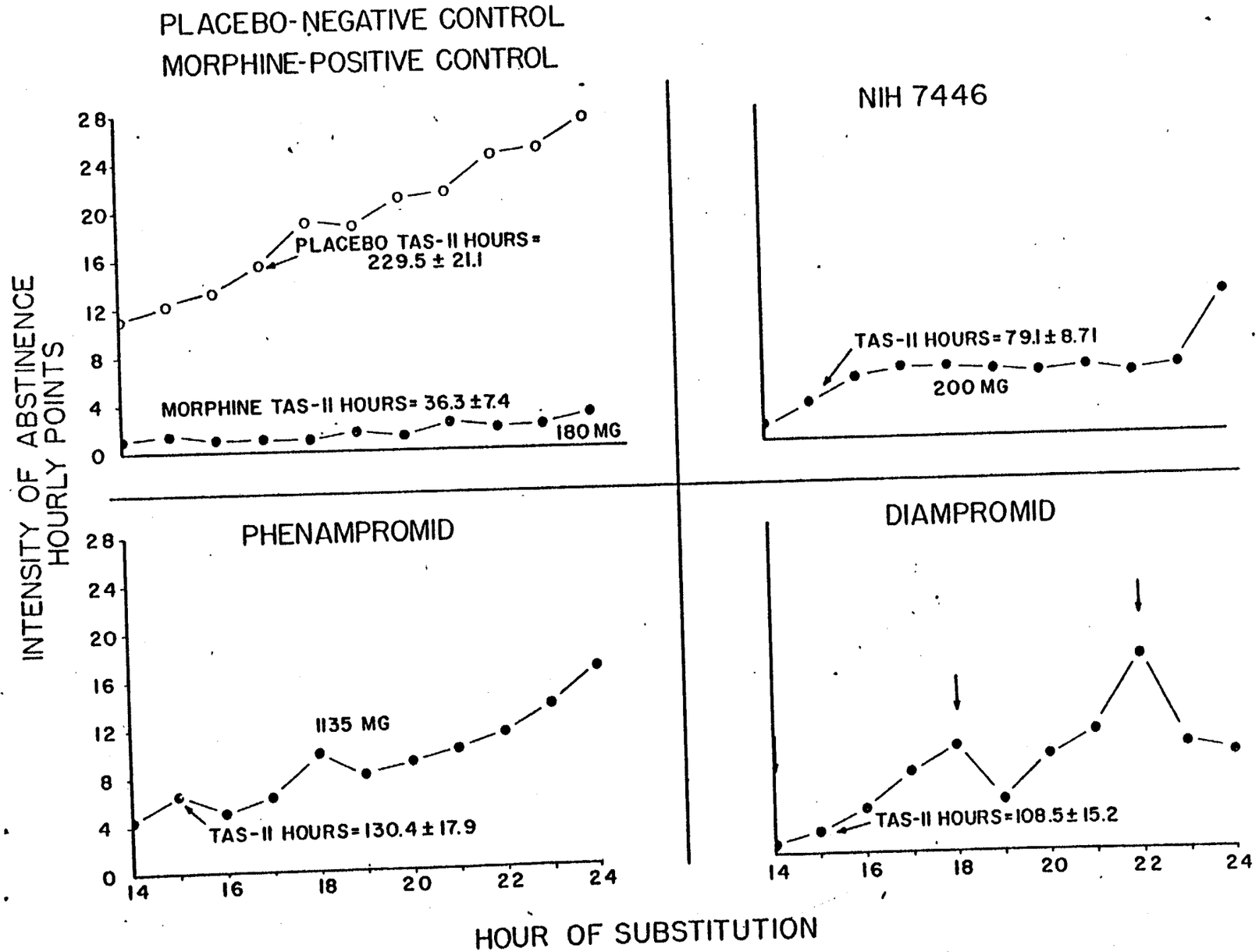
SINGLE DOSE PATIENT RATINGS OF NIH 7446 AND MORPHINE



Legend for Figure 5.

Figure 5. Comparison of average intensity of abstinence during a 24-hour substitution of (1) a placebo, (2) NIH-7446, (3) Phenampromid, (4) Diampromid, and (5) morphine, continued in the same 9 subjects addicted to morphine ~~=~~ evaluated by the "modified" Himmelsbach hourly point system. The TAS-11 values represent the total abstinence hourly scores for eleven observations, starting from the 14th and continuing through the 24th hour of abstinence, ± the standard error of the means. In the case of Diampromid, arrows indicate that medication was given immediately following the abstinence score illustrated.

B-198


PLACEBO-NEGATIVE CONTROL
MORPHINE-POSITIVE CONTROL
PLACEBO TAS-II HOURS = 229.5 ± 21.1
MORPHINE TAS-II HOURS = 36.3 ± 7.4
180 MG
NIH 7446
TAS-II HOURS = 79.1 ± 8.71
200 MG
PHENAMPROMID
1135 MG
TAS-II HOURS = 130.4 ± 17.9
DIAMPROMID
TAS-II HOURS = 108.5 ± 15.2
INTENSITY OF ABSTINENCE HOURLY POINTS
HOUR OF SUBSTITUTION
0
4
8
12
16
20
24
28
14
16
18
20
22
24